On the Physiological Activity of Substances Indirectly Related to Adrenalin.

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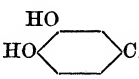
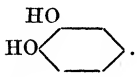
Since adrenalin itself possesses such remarkably definite physiological properties which are shared by the synthetical substance described in the preceding paper, it seemed to be of interest to try and trace some connection between their chemical structure and physiological action and, in particular, to see if the activity was to be ascribed to any particular chemical group or combination of groups.

If the formula for adrenalin be either  or  , we may artificially divide the molecule into two portions, an aromatic catechol nucleus and an oxyethylmethylamine ($CH_2OH.CH_2NHCH_3$) side-chain. The latter substance was prepared by heating glycolchlorhydrin with methylamine (1) and it was found that injection into a rabbit of quantities up to 10 milligrammes was followed by slight if any rise in blood-pressure. Injections of catechol, on the other hand, produce a great increase in pressure, as may be seen in fig. 1. This fact has also been observed by Mühlmann (2). The amount of substance required to produce an effect is considerable when compared with adrenalin, but a positive result seems significant. It will be seen from the tracing that the effect is prolonged, and it was found that subsequent injection of adrenalin produced no higher retinal pressure than that caused by catechol. When smaller quantities are injected into rabbits it is found that one does not obtain a rapid rise followed by a rapid fall, but both phases are prolonged and the stimulation is sub-maximal.

The power of causing increased blood-pressure is shared by many other substances containing the catechol nucleus. Thus the two intermediate products in the synthesis of the "adrenalin-like" base described in the preceding paper are both physiologically active. In the case of chloracetyl-

catechol several milligrammes are required to produce well-marked effects, but methylamino-acetylcatechol is more nearly related to adrenalin, and, as one would expect, is more active physiologically. The properties of this substance have been investigated by Hans Meyer (3) so that it is unnecessary to give further details, but it may be noted that about half a milligramme is necessary to produce a definite rise in blood-pressure in a rabbit, so that the activity of the substance is far inferior to that of adrenalin.

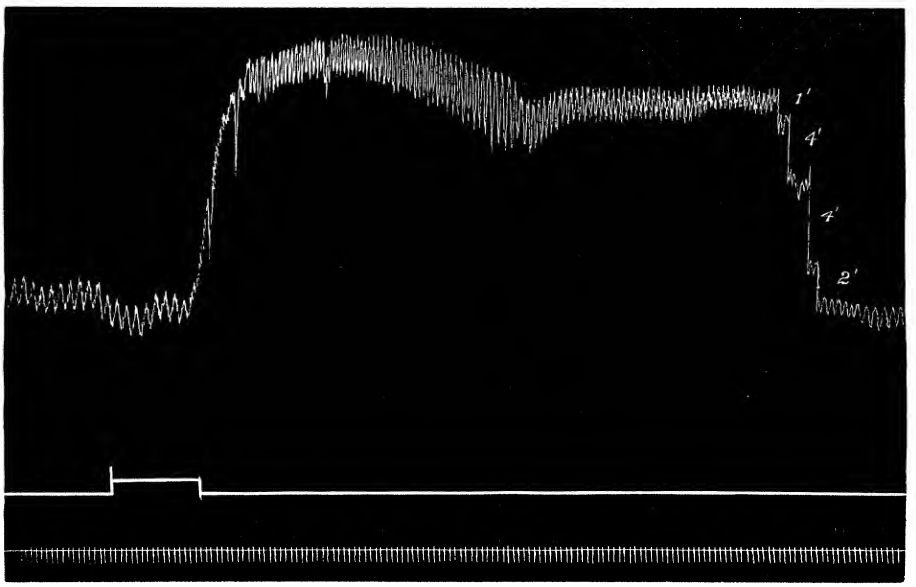


FIG. 1.—Rabbit, 2·2 kilogrammes. Carotid B. P. Vagi divided. Urethane. 10 milligrammes catechol. Zero pressure 30 mm. below signal line. Time = seconds.

If the chlorine in chloracetylcatechol be replaced by hydrogen the product acetylcatechol, $C_6H_3(OH)_2.CO.CH_3$, is still active, but if the hydrogen of the hydroxyl groups be replaced, for example, by acetyl groups the product is quite inactive. Similarly, although, as previously stated, injection of catechol is followed by increase in blood-pressures, the methyl ether of catechol, $CH_3.O.C_6H_4(OH)$, produces no such effect and other analogous cases have been observed. It may be noted that substitution of the hydrogen of the phenolic hydroxyl groups very greatly increases the chemical stability of these substances and this, one may well imagine, would tend to result in substances of less marked physiological activity. From these results it would appear that two free hydroxyl groups in the nucleus are essential constituents of active substances in this group and, since of the three isomeric dihydroxybenzenes only catechol produces a rise in blood-pressure after injection, it is possible that the hydroxyl groups must be in the *ortho* position to one

another. Further work is needed, however, before the question can be definitely decided.

As has been already stated, methylamino-acetylcatechol is fairly active in causing increased blood-pressure, whilst the activity of its reduction product is comparable with that of adrenalin. It seemed to be of interest to try the action of the amino- and other alkylamino-acetylcatechols and their reduction products. A considerable difference is noticeable in their physiological properties, corresponding to differences in chemical structure. Thus, amino-acetylcatechol ($C_6H_3(OH)_2.CO.CH_2NH_2$), and the lower alkylamino-acetylcatechols, *e.g.*, the ethyl and di-methyl derivatives, closely resemble the methylamino-acetylcatechol previously described, and their reduction products are very active.

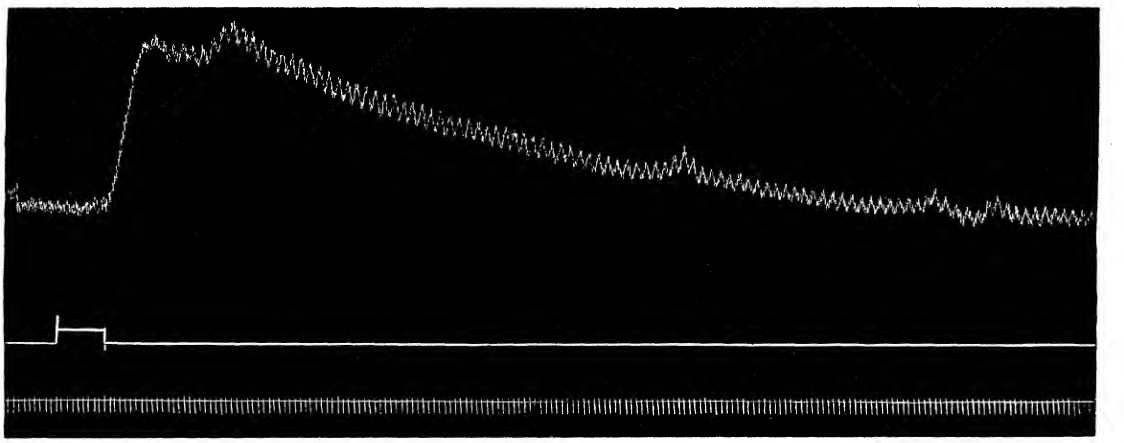
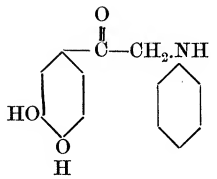


FIG. 2.—Rabbit, 2·5 kilogrammes. Carotid B. P. Vagi divided. Urethane. 0·0010 gramme hydrochloride of ethylamino-acetylcatechol. Zero pressure 30 mm. below signal line. Time = seconds.

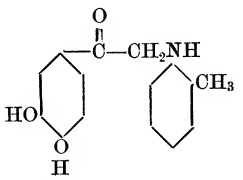
If, however, one takes a higher member of the same series, *e.g.*, heptylamino-acetylcatechol, $C_6H_3(OH)_2.CO.CH_2NH(CH_2)_6.CH_3$, it is found that whilst the ketone base is still active, yet on reduction its activity is but slightly increased.

The base was prepared by the action of excess of heptylamine upon the di-acetyl derivative of chloracetylcatechol, and is a white crystalline substance melting at 125°, and giving beautifully crystalline salts.

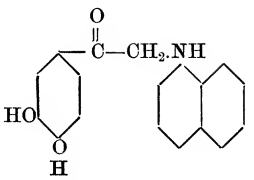
This result shows that the nature of the alkyl group attached to the nitrogen atom is of great importance. If, instead of an aliphatic one substitutes an aromatic group attached to the nitrogen atom the changes in physiological properties are very marked. The following bases were examined :—



Anilino-acetylcatechol (4).



o-Toluidino-acetylcatechol (4).



α-Naphthylamino-acetylcatechol.

None of these bases produced a decided rise in blood-pressure on injection of small quantities. Usually, a fall in pressure was noted, which was least marked with the first substance, and was in this case sometimes followed by a slight rise. This rise was more marked when the substance obtained by its reduction was injected, but even then its activity was far behind the simpler alkylamino derivatives.

As the aromatic bases are only very sparingly soluble in water, they were dissolved in weak alcohol for purposes of injection. Control experiments without the bases were made with satisfactory results. The α-naphthylamino-acetylcatechol has not been previously described and was prepared by acting upon chloracetylcatechol (1 mol.) with α-naphthylamine (2 mols.) and a little alcohol. It is a faintly yellowish-green coloured crystalline substance, sparingly soluble in dilute spirit and is a very feeble base.

A base ($C_6H_3(OH)_2.CO.CH_2NH.CH_2.C_6H_5$), which may be regarded as intermediate between the two chemical types already described, was obtained by the action of benzylamine upon chloracetylcatechol. The substance is crystalline and readily soluble in alcohol. It had very little effect on the blood-pressure in rabbits, even when injected in fairly large quantities.

Another kind of base was prepared by acting upon chloracetylcatechol with tertiary bases. For example, aqueous tri-methylamine (1 mol.) was digested with chloracetycatechol for some hours, and after adding a drop or two of dilute hydrochloric acid the solution was concentrated and crystallised. Purification is readily carried out by solution in alcohol and precipitation with ether. The substance has the formula $C_6H_3(OH)_2.C = O.CH_2N(CH_3)_3Cl$.

It was found to be *more* active than the corresponding mono-methylamine derivative from which the "adrenalin-like" substance was obtained. In the case of rabbits, so small a quantity as 0·00002 gramme may produce a marked rise. In the comparatively few experiments which were made, it appeared that the substance was very rapidly destroyed after injection, as when quite large quantities were employed the effect was scarcely more prolonged than when the minimal amount necessary to produce maximal stimulation was used.

The reduction of the tri-methylamine derivative did not give products of

much increased activity, thus differing in this respect very distinctly from the mono-alkylamine derivatives.

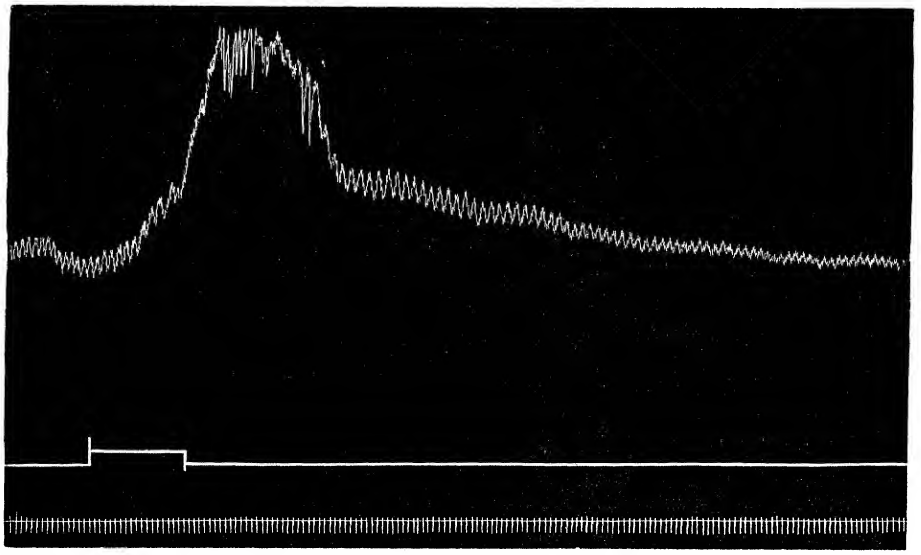
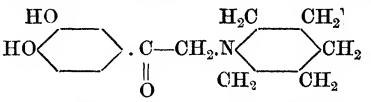


FIG. 3.—Rabbit, 2·5 kilogrammes. Carotid B. P. Vagi divided. Urethane. 0·0005 gramme $C_6H_3(OH)_2.CO.CH_2N(CH_3)_3Cl$. Zero pressure 40 mm. below signal line. Time = seconds.

A corresponding base in the aromatic series was prepared from dimethylaniline and chloracetylcatechol, but, like the other aromatic bases, was not effective in producing rise in blood-pressure.

It is well known that injection of piperidine is followed by increase in blood-pressure (5), and it therefore seemed conceivable that if instead of the ordinary amines used in preparing the bases already described, piperidine was substituted, one might obtain products with increased activity. Experiments, however, showed that this was not the case. Piperidino-acetylcatechol,



, was found to be decidedly less active than the corresponding methylamine derivative, and its activity was scarcely increased upon reduction.

It is obvious that the experiments recorded, although ranging over a number of different types of substances, are very incomplete, yet they seem to warrant certain conclusions, and to indicate the lines upon which one must proceed if one wishes to synthesise substances whose physiological properties more or less closely approximate to those of natural adrenalin.

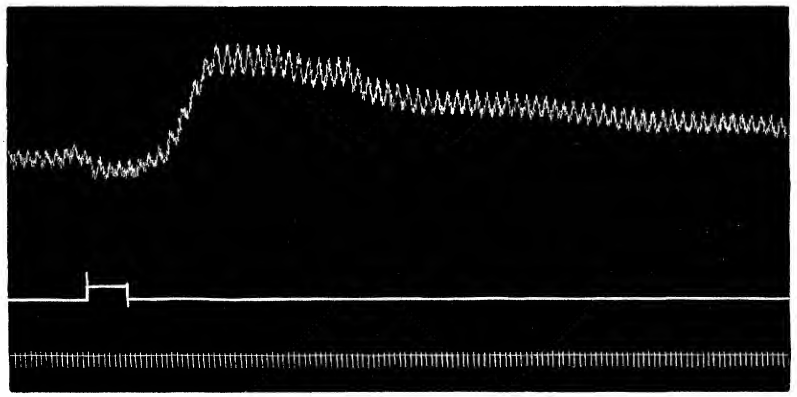


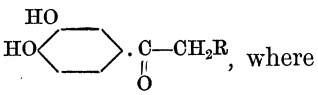
FIG. 4.—Rabbit, 2·5 kilogrammes. Carotid B. P. Vagi divided. Urethane. 0·005 gramme piperidino-acetylcatechol as hydrochloride. Zero pressure 30 mm. below signal line. Time = seconds.

The following deductions are made provisionally, until further experimental evidence is available:—

(i) It appears that the catechol nucleus is essential for the production of physiologically active substances of the type of adrenalin.

(ii) It is of importance that the hydrogen atoms of both hydroxyl groups in the catechol nucleus be unsubstituted.

(iii) An alkyl group of low molecular weight (*e.g.*, methyl, ethyl) attached to the nitrogen tends to produce a much more active substance than when an aromatic group is attached, whilst derivatives of piperidine, heptylamine, and benzylamine occupy an intermediate position.

(iv) The reduction of ketonic bases of the type  , where R is a simple aliphatic group, results in the production of bases with enormously increased physiological activity.

(v) In the substances examined there appears to be a connection between chemical instability and physiological activity, and *vice versâ*.

In conclusion I wish to acknowledge my indebtedness to the Research Fund Committee of the Chemical Society for a grant which has partly defrayed the expenses of the work described in this and the preceding paper.

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(5) Tunnicliffe, 'Centralblatt. f. Physiologie,' vol. 10, p. 777, 1897; Moore, 'Jour Physiol.,' vol. 22, p. 273, 1897.